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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,628	01/26/2004	Veronique Trochon	1002-04	9953

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,628	TROCHON ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2006*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2 and 4-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Any rejection of record in the previous action not addressed in this office action is withdrawn. The new grounds of rejection herein were necessitated by amendment and, therefore, this action is final.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 4-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment.**

The limitation that "the disintegrin domain contains an RGD sequence" has been added to claims. Hence, the method is limited to nucleic acids encoding a polypeptide or derivatives comprising an RGD sequence, for which the examiner has not been able to find support in the specification. The specification teaches in relation to an RGD sequence, "both AMEP and the 1.4-kDa peptide possess an RGD sequence implicated in bonding endothelial cells to alpha v beta 3 integrins, we believe that the action of AMEP is not limited to blocking the functions of the alpha v beta 3 integrin. AMEP appears to possess its own activity which could be linked to modifications of the signalization at the cellular level (message that could be transported by the

integrin alpha v beta 3 and/or metargidin)." This passage suggests that while AMEP, the molecule used in the methods of the instant invention possesses an RGD sequence; its function appears to involve other processes then that mediated by RGD. In fact, there is no requirement in the specification that the disintegrin domain must comprise specifically an RGD sequence. Therefore, the limitation of adding, "the disintegrin domain contains an RGD sequence" is impermissible NEW MATTER.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 4-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering and expressing the disintegrin domain, which is Met 420 to Gly 511 of SEQ ID NO: 1 at a site to be targeted for diminution of the number of intratumoral vessels, for inhibition of growth of melanoma and for inhibition of pulmonary metastases, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 7/28/06 and restated below. The rejection has been slightly reworded based upon applicants' amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The instant claims are drawn to a methods of inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis by administration of a nucleic acid encoding a polypeptide comprising all or part of a disintegrin domain of an adamalysin or a derivative.

2) Scope of the invention. The number of disease and conditions to be treated is of extremely broad scope. Each of the claims recite a single step of "administering a therapeutically effective amount of an active" of the nucleic acid. The specific adamalysin to be used is metargidin, which is disclosed as SEQ ID NO: 1. The derivative must code for all or part of the disintegrin domain as long as the peptide comprises RGD and inhibits migration and proliferation of endothelial cells, adhesion of endothelial cells to matrix substrates and formation of capillary structures.

3) State of the art. The adamalysin family functions in proteolysis, adhesion, fusion and intracellular signaling (see Ruben et al, US 2002/0182702 ¶ 1042). The art teaches that there are two subfamilies of adamalysins 1) snake venom metalloproteases (SVMPs) and 2) the ADAMS

(proteins with a disintegrin domain and a metalloprotease domain). Multiple ADAMS have been identified including ADAM1, ADAMTS-1, fertilin (ADAM2), cryitestin (ADAM3), epididymal apical protein I, meltrin, MS2, TNF-a converting enzyme, Kusbanian and metargidin (see Ruben et al, ¶ 0004). Within the ADAMS, the disintegrin domain functions to prevent integrin-mediated cell to cell and cell to matrix interactions such as plated aggregration, adhesion, migration of tumor cells or neutrophils or angiogenesis. There have been multiple propositions that members of the adamalysin family have a potential to treat a myriad of conditions such as those recited here (see Ruben et al US 2002/0165377 and Young et al (US 2003/0194797 in which the role of ADAM-22 and any other ADAM protein in inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis is proposed), but these propositions have not lead to the identification of any treatments that are viable options against diseases.

4) Guidance in the specification. The specification states that metargidin comprises AMEP (anti-angiogenic metargidin peptide) and is a human protein with multipotent function including blocking angiogenic functions of integrin alpha v beta, inhibition of migration and formation of capillary structures and functions proapototically independent of modification of their cell cycle. The disintegrin domain constitutes Met 420 to Gly 511 of SEQ ID NO:1. As to derivatives, the specification teaches (¶ 0039), "The derivatives can be fragments of truncated form, sequences modified by deletion, addition, suppression or replacement of one or more amino acids. The derivatives can also be fragments corresponding to said derivatives constituted by chemically modified amino acids, these modifications making the derivatives more stable.

The invention also pertains to polynucleotide sequences coding for said derivatives". Applicants have limited the derivatives to those that comprise RGD. Applicants synthesize AMEP in bacteria and demonstrate that this protein can function to inhibit adhesion of fibrinogen to vitronectin and fibronectin, inhibit endothelial cell migration, proliferation, capillary formation and stimulates proapoptosis in endothelial cells *in vitro*. *In vivo,* AMEP nucleic acid was electrotransferred to muscle of nude and C57B1/6 mice and inhibited growth of MDA-MB-231 tumor growth and formation of pulmonary metastases in syngeneic mice.

5) **Unpredictability of the art.** The enablement of the instant invention has been assessed in light of the specification and the prior art available at the time of filing. "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the instant case, there are multiple inoperative embodiments when considering the use of the instant invention in humans such as 1) applicants recite a broad and diverse range of ailments that are to be treated and conditions that are to be inhibited by use of any or all of a disintegrin domain from any adamalysin or derivative thereof as long as the derivative comprises an RGD domain and 2) the lack of recited route of administration of the nucleic acid exacerbate the unpredictability of the art. In light of the art at the time of filing, the instant invention would require undue experimentation to perform the invention in humans.

The instant invention is unpredictable for inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis in humans for the following reasons. First, applicants' invention is based upon the premise that the disintegrin domain of amadalysin can be used therapeutically to treat a variety of conditions. The claims are directed to a broad and diverse genus of disintegrin parts, complement and derivatives molecules from any adamalysin. However, the specification teaches (¶ 0032), "The physiological role of the different adamalysins is extremely varied: regulation of cell adherence, release of a ligand, activation of a receptor, cell fusion (review, Primakoff and Myles, 2000). However, the mode of action of these molecules remains unknown" (emphasis added). The specification is directed specifically to the analysis of AMEP, the disintegrin domain of metargidin encoded by Met 420 to Gly 511 of SEQ ID NO:1. As well, the invention is practiced using this peptide and the results do not demonstrate any understanding of the mode of action or the general nature of the effects of AMEP, (¶ 0093) "The set of results obtained show that AMEP possesses an antiangiogenic activity that is greater than that of the 1.4-kDa peptide. Given that both AMEP and the 1.4-kDa peptide possess an RGD sequence implicated in bonding endothelial cells to alpha v beta 3 integrins, we believe that the action of AMEP is not limited to blocking the functions of the alpha v beta 3 integrin. AMEP appears to possess its own activity which could be linked to modifications of the signalization at the cellular level (message that could be transported by the integrin alpha v beta 3 and/or metargidin)." The disclosure does not provide adequate guidance for the use of any part of any derivative of any disintegrin domain from any adamalysin and hence the recited goals are highly unpredictable. Therefore, the efficacy of the instant invention

lies in the use Met 420 to Gly 511 of SEQ ID NO:1 and while the structural requirements for this peptide alone have been demonstrated, the specification has not demonstrated what amino acids, sequences or regions can be altered to mediate the same activity. Applicants do not demonstrate nor is it known in the art that this peptide can mediate all of the recited functions. The claims recite that the broad genus of disintegrin adamalysin sequences can inhibit angiogenesis, invasion or formation of metastases and yet applicants have only demonstrated that the number of intratumoral vessels can be reduced. Applicants recite that these sequences can treat cancer, inflammatory disease, atherosclerosis, macular degeneration and psoriasis. Of these, applicants have demonstrated that tumor growth alone can be inhibited. As well, the mechanism of action (or actual functional requirements) are unknown which exacerbates the ability to identify those sub regions required to mediate the function that leads to the effects noted in the application.

Secondly, the method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma et al speak to the problem that is confronted in the art when they teach (Verma and Somia, Nature, September 1997), "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression". To present date, no generic mode of gene transfer has provided a viable option for successful gene therapy protocols, which exacerbates the broad and diverse treatments proposed by applicants.

6) **Summary**. The invention recites broadly a method of inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating

atherosclerosis, treating macular degeneration or treating psoriasis using a broad genus of molecules. The unpredictability of using the claimed invention for all of these methods is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established protocols and the inability to predict successful administration of the broad genus of molecules: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C.112, first paragraph on pages 8-12 of the amendment filed 10/31/06. Applicants' arguments filed 10/31/06 have been fully considered but they are not persuasive for the following reasons.

Applicants demonstrate that AMEP or Met420-Glu511 of SEQ ID NO:1 (metargidin) can function to inhibit adhesion of fibrinogen to vitronectin and fibronectin, inhibit endothelial cell migration, proliferation, capillary formation and stimulates proapoptosis in endothelial cells *in vitro* and i*n vivo,* inhibited growth of MDA-MB-231 tumor growth and formation of pulmonary metastases in syngeneic mice. However, the claims are broadly drawn to use of any disintegrin

domain from any adamalysin in methods of inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis. First, the art teaches that adamalysins are a broad and diverse genus of peptides that include metargidin (see Ruben et al, ¶ 0004). The art does not demonstrate and applicants' specification argues against a universal structure or function of any adamalysin. In fact, as reviewed in Primakoff and Myles, 2000, "The physiological role of the different adamalysins is extremely varied: regulation of cell adherence, release of a ligand, activation of a receptor, cell fusion. However, the mode of action of these molecules remains unknown" (emphasis added).

Secondly, the claims still encompass a broad and diverse genus of molecules only linked by occurrence of an RGD domain. To this end, applicants have not demonstrated that use of the RGD domain alone is all that is required for activity. Rather AMEP is required for protein function. The art teaches that even minute changes in the protein sequence can affect protein function. The ability to determine *a priori* whether a derivative can function in the recited invention is not a high art. A particular protein sequence determines the protein's structural, and functional properties, and a predictability of a representative number of claimed polypeptide sequences that display noteworthy biological properties requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its functional usefulness (see Tertiary structure, Protein structure prediction and Smith et al). Applicants argue that ADAM-9, ADAM-12 and ADAM-23 have the capacity to bind to integrins via their disintegrin domain and applicants have

disclosed that RGD-containing domain of adamalysin have antiangiogenic and antimetastatic activities. Hence, it appears that applicants' claims are enabled for use of the disintegrin domain of RGD-containing adamalysins but not for any disintegrin domain from any adamalysin or any derivative that happens to include RGD.

Thirdly, applicants argue that the methods have been demonstrated using polynucleotides that have produced a therapeutic response in animal models. However, use of xenograft mice models has not been demonstrated to be an art recognized model even for limited use of cancer treatment in humans as demonstrated by Gura et al. A study by National Cancer Institute demonstrated that using xenograft models do not handle drugs in the same way that the human body does and cell culture provides no information about whether a drug will make it to target sites or not (see e.g. Gura, Science, page 1041, col 1). Ultimately the xenograft model system identifies agents that are effective in treating mice but not humans (see e.g. page 1041, col 2, last paragraph). Furthermore, in considering whether the provided mouse reasonably correlates with the ability to perform the method in humans, it must be considered that applicants have recited multiple diseases including angiogenesis, metastases, cancer, inflammatory diseases, atherosclerosis, macular degeneration or psoriasis. It cannot be reasonably concluded that the xenograft model with hepatocellular carcinoma functions as a correlative model for all of these diseases. While the teachings of Verma et al date back to 1997, these teachings are still relevant today as the obstacles to delivery of nucleic acid to humans for treatment of disease still remains a problem.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2 and 4-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Ruben et al (US 2002/0165377; see entire document). **This rejection is maintained for reasons of record in the office action mailed 7/28/06 and restated below.**

Rubens et al teach treatment of medical conditions using Adam polynucleotides (¶ 0420) such as angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis (see ¶ 0084-0083). According to ¶ 0004, a ADAM protein includes metargidin. While SEQ ID NO:1 is not disclosed, the ADAM molecules are related such that a derivative of SEQ ID NO;1 is encompassed by the molecules disclosed in Rubens et al. Cells are transformed with vectors comprising the genes to express the disintegrin domain (see e.g. ¶ 0179-0183).

Claims 1, 2 and 4-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Fanslow et al (US 2006/0177443; see entire document). **This is a new rejection necessitated by applicants' amendment.**

Fanslow et al teach treatment of medical conditions using Adam –15 or metargidin polynucleotides (¶ 0041) such as angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or

treating psoriasis (see ¶ 0065-0070). While SEQ ID NO:1 is not disclosed, the ADAM-15 include RGD and are related such that a derivative of SEQ ID NO;1 is encompassed by the molecules disclosed in Fanslow et al (¶ 0007).

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 102 on pages of the amendment filed 10/31/06. Applicants' arguments filed 10/31/06 have been fully considered but they are not persuasive for the following reasons. Rubens et al disclose generally use of ADAMS proteins, that include metargidin. Metargidin comprises an RGD domain (in fact this is the protein disclosed in the instant specification) and thus meets the limitations of the instant claims. Thus this protein inherently comprises the properties as recited. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable." (MPEP 2105, I).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

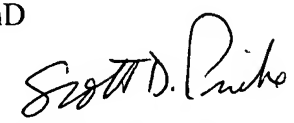
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633



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